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1635

DATE MAILED: 10/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/604,340

Applicant(s)

HILDINGER ET AL.

Examiner

Jon B. Ashen

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 July 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-50 is/are pending in the application.
- 4a) Of the above claim(s) 7,9,16-18,23,33,34,37 and 40-48 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6,12-15,19-22,24-32,35,36,38,39,49 and 50 is/are rejected.
- 7) ☒ Claim(s) 3-6,8,10-12,19,20,22,25,28-32,35,36,38 and 39 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 7/03.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, c (short hairpin RNAs) in the reply filed on 7/14/05 is acknowledged. Applicant's arguments are persuasive with regards to the species relationship of the inventions identified in the Action mailed 6/17/05 as Group I a and c (see remarks pg. 4 of the response filed 7/14/05). However, with regard to Group I, b, Applicant's arguments are not persuasive because, although the ultimate biological mechanism of particular double stranded RNAs may be to mediate RNA interference (RNAi), the instant claims are drawn to methods that require administration of particular vectors that express particular compounds wherein each method requires administration of either a single vector (Group I, a and c) or multiple vectors (Group I, b). The method of Group I, b, requires additional method steps not required by either of Group I, a or c, specifically, dual transfection protocols wherein multiple vectors are administered *in vivo*, these steps not being required for the other inventions. A search of Group I a and c, together with Group I b, would impose a serious and undue burden on the Examiner in terms of search and examination because a search of the method steps required for each invention would not be coextensive. Applicant's argument that a search strategy designed to search all inventions at once might be more difficult, including a presentation of a brief search strategy by Applicant, is not persuasive because individual search strategies will vary depending on the searcher, i.e., will be designed by the person performing the search and will not be limited to keywords proposed by Applicant.

Therefore, upon further consideration, the elected invention identified as Group I c will be examined as a patentably distinct species of method, within the elected group I and will be examined as a species election as follows.

Applicant is considered to have elected a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1, 2 and 2 are generic to both Group I a and Group I, c. Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

The requirement for restriction between the inventions identified as Group I, a and c and Group I, b, is still deemed proper and is therefore made FINAL.

Status of the Application

2. Claims 1-50 are pending in this application. Claims 7, 9, 16-18, 23, 33-34, 37 and 40-48 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/14/05. Claims 1-6, 8, 10-15, 19-22, 24-32, 35-36, 38-39, 49 and 50, drawn to the Invention of Group I, elected species c (for the reasons set forth above) and VEGF (as set forth in amended claim 36) are currently under examination.

Claim Objections

3. Claims 8, 10 and 11 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims not been further treated on the merits.

4. Claims 3-6, 12, 19-20, 22, 25, 28-32, 35-36, 38 and 39 are objected to because of the following informalities: Each of the above claims is drawn to the method of "claim 1 and 2" but should refer, as multiple dependent claims, to "claims 1 or 2"; i.e., in the alternative. Appropriate correction is required.

5. Claims 2, 6, 19 and 20 are objected to because of the following informalities:
Claims 2, 6 and 20 each recite, “(at least)” which is offset by parentheses. Claim 19 recites “(internally)” which is offset by parentheses. Based on the offset of these terms within the claims, the Examiner cannot determine if this text is required by the claim or optional within the claim. The removal of either the text, in the event that it is optional, or of the parentheses, in the event that it is not, would be remedial. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-6, 12, 19-20, 22, 25, 28-32, 35-36, 38 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 2 are drawn to a method of decreasing the expression of a target gene in a mammalian subject comprising administering a therapeutically effective amount of an RNAi expression cassette that is a recombinant adeno-associated viral vector to “suitable target cells” which results in expression of the RNAi cassette. However, the terminology, “suitable target cells” is relative terminology within the context of this claim. The skilled artisan cannot determine the metes and bounds of what would constitute a “suitable target cell” because there is no way to determine what the cells would be suitable for or what a suitable target cell would be for a target gene that is any target

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gene in any cell. Claims 4-6, 12, 19-20, 22, 25, 28, 29-32, 35-36, 38 and 39 are rejected due to their dependence on a rejected claim.

8. Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 3 recites the limitation "the RNA coding region", in lines 1 and 4. There is insufficient antecedent basis for this limitation in the claim. In particular, the metes and bounds of what is being claimed by "the RNA coding region" cannot be determined because this terminology does not appear in claims 1 and 2, from which the instant claim depends, and no assumption can be made as to what is intended to be encompassed by this terminology.

9. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 5 is drawn to a method of treatment that requires an RNAi expression cassette that encodes "one or more RNA molecules which are capable of forming an RNA interference inducing double stranded RNA complex" which is interpreted as reading on the RNAi induced silencing complex or RISC complex. However, it is not clear how an RNA molecule as claimed, can encode an RNA molecule that is capable of forming a RISC complex because the RISC complex comprises both the dsRNA trigger and associated proteins that are not claimed as being encoded by the RNAi expression cassette that is required by the instant methods. The

metes and bounds of what is being claimed with this terminology cannot be determined by the skilled artisan, rendering this claim indefinite. Removal of the word complex, which imparts ambiguity to the instant claim, would be remedial.

10. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 21, which depends from claim 19, recites the limitation "wherein the two nucleotide sequences of said RNA molecule", in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim. In particular, the metes and bounds of what is being claimed cannot be determined because although reference is made to "two (internally) complementary nucleotide regions" in claim 19, no assumption can be made as to what is intended to be encompassed by this terminology or that that the regions in claim 19, that are required to be internally complementary, are the "two nucleotide sequences" that are required in claim 21.

11. Claim 27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 27 recites, "wherein the third portion of said linear RNA molecule promotes hybridization between the first and second portion." However, the skilled artisan cannot determine the metes and bounds of what is encompassed by the terminology of "promotes hybridization" within the context of this claim. Does this terminology mean that the third portion is required to hybridize to itself, thereby

promoting hybridization between the first and second portion? Does this terminology mean that the third portion promotes hybridization of the first portion to the second portion?

12. Claim 29 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 29 recites the limitation "the second sequence of said linear molecule" in lines 1 and 2. There is insufficient antecedent basis for this limitation in the claim because this claim depends from claim 22 which does not contain the terminology "the second sequence" or "linear molecule".

13. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 39 recites, "wherein the transduced cells are cells of and/or in the eye, retinal cells*(text listing cells and organs omitted by the Examiner)* and/or brain cells." However, as written the metes and bounds of what is being claimed cannot be determined by the skilled artisan because this claim is reasonably read as claiming, wherein said transduced cells are cells of and in retinal cells, cells of and in photoreceptor cells, etc. Additionally, as written this claim is reasonably read as, wherein said transduced cells are cells of and in the eye and in brain cells. In the instant case it is not clear how cells can be in other cells or what this would encompass.

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1-6, 12-15, 19-22, 24-32, 35-36, 38-39, 49 and 50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 1 and 2 of the instant invention are broadly drawn to a method of decreasing the expression of a target gene in a mammalian subject comprising administering a therapeutically effective amount of an RNAi expression cassette that is a recombinant adeno-associated viral vector to "suitable target cells" which results in expression of the RNAi cassette which leads "directly or indirectly" to a decrease in expression of the RNAi target gene. Subsequently dependent claim 19 is broadly drawn and reads on an RNA molecule that when expressed from the RNAi expression cassette reduces the intracellular concentration of the target mRNA or "any substantially similar endogenous mRNA. Subsequently dependent claim 31 requires that the rAAV vector be of a serotype of any one of serotypes 1-8 or "any homologous serotypes or hybrids thereof. Subsequently dependent claim 35 requires that the RNAi target gene is one that "is likely to cause disease." Claim 49 is drawn to a method of treating a

mammalian subject with an autosomal-dominant disorder or "other disease including cancer and infectious diseases" by administering an rAAV vector to initiate decrease of a RNAi target gene using RNAi to achieve post transcriptional gene silencing.

Claims 1 and 2, and all claims which depend from claims 1 and 2, read on a broad genus of method that employs an RNAi expression cassette, the product of which will lead "indirectly" to a decrease of expression of a target gene, which can be any gene, in "suitable target cells" that can be any cells. Claim 19 reads broadly on a genus of method that requires an RNA molecule that when expressed from the RNAi expression cassette reduces the intracellular concentration of the target mRNA or "any substantially similar endogenous mRNA. Claim 31 reads broadly on a method that requires an rAAV vector of any one of serotypes 1-8 or "any homologous serotypes or hybrids thereof. Claim 35 reads broadly on a genus of method that requires decrease in expression of a RNAi target gene is one that "is likely to cause disease" and claim 49 reads broadly on a method of using an rAAV vector to provide a treatment of essentially any disease by initiating a decrease of a RNAi target gene.

However, the specification as filed does not provide an adequate written description of the broad genera of methods identified above that will function to transduce "suitable target cells", lead "indirectly" to a decrease of expression of a target gene or that will express an RNA molecule which reduces the intracellular concentration of a target mRNA or "any substantially similar endogenous mRNA," commensurate with what is now claimed. Additionally, the specification as filed does not provide an adequate written description of the broad genera of methods that require an rAAV

vector of any one of serotypes 1-8 or "any homologous serotypes or hybrids thereof," of a genus of method that requires decrease in expression of a RNAi target gene is one that "is likely to cause disease" or of a method of using an rAAV vector to provide a treatment of essentially any disease by initiating a decrease of a RNAi target gene that will function, commensurate with what is now claimed, as a method that employs any rAAV vector of one of serotypes 1-8 or "any homologous serotypes or hybrids thereof," to target any gene that is "likely to cause disease" or to treat essentially any disease by initiating a decrease of a RNAi target gene, wherein the disease is any disease and the target gene any target gene.

The specification as filed provides no definition of "suitable target cells" that contain target genes the expression of which is reduced "indirectly" or of what is encompassed by a target mRNA or "any substantially similar endogenous mRNA." The specification as filed provides only general guidance as to what is contemplated as a target gene wherein it states, "The RNAi target gene does not limit the scope of this invention and may be any gene derived from the cell: an endogenous gene, a transgene, or a gene of a pathogen that is present in the cell after infection thereof. Thus, the choice of the RNAi target gene is not limiting for the present invention: The artisan will know how to design an RNAi expression cassette to down-regulate the gene expression of any RNAi target gene of interest. Depending on the particular RNAi target gene and the dose of rAAV virions delivered, the procedure may provide partial or complete loss of function for the RNAi target gene (section [0114])." However the disclosure of the specification does not indicate that Applicant was in possession of the

broadly claimed genera above nor does it provide specific guidance that would lead the skilled artisan to recognize that applicant in possession of a method that would express an RNA in "suitable target cells" that are any cells, that would lead, "indirectly" to the decrease in expression of a target gene that can be any target gene or that will target something that is any target gene or "any substantially similar endogenous mRNA."

Additionally, the specification as filed provides no limiting definition and only general guidance as to what is encompassed by "any homologous serotypes or hybrids thereof," of rAAV vectors of serotypes 1-8, of an RNAi target gene is one that "is likely to cause disease" or of a method of using an rAAV vector to provide a treatment of essentially any disease by initiating a decrease of a RNAi target gene that would indicate that Applicant was in possession of such broadly claimed genera.

The specification provides only general guidance in regards to the structure "any homologous serotypes or hybrids thereof," of rAAV vectors of serotypes 1-8 that will target and decrease expression of any RNAi target gene, no guidance in regards to target genes that are "likely to cause disease" and no guidance as to how the skilled artisan would treat essentially any disease or infection, as claimed. The specification discloses only examples of methods wherein RNA expressed from rAAV vectors decreases expression of a luciferase reporter transgene that has been introduced to various organs and tissues of mice by rAAV transduction and no examples of a decrease in expression of any endogenous genes.

Therefore, in disclosing only broad and general guidance in regards to what is encompassed by the broad genera set forth above, the specification does not provide a

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correlation between the structure of the rAAV vectors that are any one of serotypes 1-8 or "any homologous serotypes or hybrids thereof" that will transduce any "suitable target cells" and lead "indirectly" to a decrease in gene expression of any target mRNA or "any substantially similar endogenous mRNA" that is "likely to cause disease" which can be essentially any disease, so as to provide a treatment as claimed. Additionally, the specification as filed does not disclose any distinguishing identifying characteristics of the claimed rAAV vectors that are any one of serotypes 1-8 or "any homologous serotypes or hybrids thereof," the claimed "suitable target cells," or the claimed genes that lead "indirectly" to a decrease in gene expression of any target mRNA or "any substantially similar endogenous mRNA" that are "likely to cause disease" which can be essentially any disease, so as to provide a treatment as claimed.

The specification does not provide the specific guidance that would be required to reasonably lead one of skill in the art to the instant invention or that would allow the skilled artisan to recognize that Applicant was in possession of the instant invention, commensurate with the tremendous breadth of what is now claimed: that will function to provide expression rAAV vectors that are any one of serotypes 1-8 or "any homologous serotypes or hybrids thereof" that will transduce any "suitable target cells" and lead "indirectly" to a decrease in gene expression of any target mRNA or "any substantially similar endogenous mRNA" that is "likely to cause disease" which can be essentially any disease, so as to provide a treatment.

MPEP § 2163[R-2] I. states:

To satisfy the written description requirement, a patent specification must describe the

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claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. See, e.g., > Moba, B.V. v. Diamond Automation, Inc., 325 F.3d 1306, 1319, 66 USPQ2d 1429, 1438 (Fed. Cir. 2003); < Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563, 19 USPQ2d at 1116.

The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc., 935 F.2d at 1563-64, 19 USPQ2d at 1117.

Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Elecs., Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406; Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it").

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. > Enzo Biochem, 323 F.3d at 964, 63 USPQ2d at 1613.<

In the instant case, Applicant has not provided adequate written description of their invention because the specification does not convey, with reasonable clarity to those of skill in the art, as of the filing date sought, that applicant was in possession of the broadly claimed genera of methods of treating essentially any disease, which require broadly claimed genera of RNA molecules and rAAV vectors, as now claimed. Applicant has not shown how the invention was "ready for patenting" such as by the disclosure of expression rAAV vectors that are any one of serotypes 1-8 or "any homologous serotypes or hybrids thereof" that will transduce any "suitable target cells" and lead "indirectly" to a decrease in gene expression of any target mRNA or "any substantially similar endogenous mRNA" that is "likely to cause disease" which can be

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essentially any disease, so as to provide a treatment commensurate with the breadth of what is now claimed (that shows that the claimed invention was complete), or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the broad methods that are drawn to or require the broad genera outlined above and now claimed.

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-6, 12-15, 19-22, 24-32, 35-36, 38-39, 49 and 50 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of inhibiting the expression, *in vivo*, in a mouse, of a rAAV 2/5 delivered *luc* reporter transgene via administration of an rAAV 2/5 vector comprising an RNAi expression cassette that expresses an RNA molecule that mediates RNAi interference and subsequent mRNA degradation of the equivalently delivered *luc* reporter gene; i.e., by direct injection to the muscle, eye, brain, administration to the liver via blood stream injection and administration to the lung by inhalant, does not reasonably provide enablement for the full scope of what is now claimed, which are methods of inhibiting the expression, *in vivo*, of any gene in any mammal, including humans, via administration of any rAAV vector of serotype 1-8 or any homologous serotype or hybrid thereof comprising an RNAi expression cassette that expresses an RNA molecule that mediates RNAi interference and subsequent mRNA degradation of any endogenous

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mRNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

Instant claims 1 and 2 are extremely broad and drawn to methods of treatment *in vivo* in mammals comprising delivery to, cells of a subject, an rAAV vector which allows expression of an RNA molecule that mediates RNA interference, thereby decreasing the expression of any target gene in a mammalian subject to provide a treatment for essentially any disease. Subsequent dependent claims require further limitations in regards to the structure of and type of rAAV vector employed for delivery *in vivo*, the structure of the RNA molecule to be expressed *in vivo*, specific promoters to be included in the rAAV vectors and particular cells that are transduced, *in vivo*. Overall, the claims of the instant application are drawn to and read on a form of nucleic acid therapy and are subject to the same considerations and limitations as other types of nucleic acid therapeutics (as discussed further below).

In regards to the amount of direction provided by Applicant as to how one of skill in the art would practice the full scope of the claimed invention, the specification as filed discloses examples demonstrating the inhibition of expression, *in vivo*, in a mouse, of a rAAV 2/5 delivered *luc* reporter transgene comprising administration of an rAAV 2/5 vector comprising an RNAi expression cassette that expresses an RNA molecule that mediates RNAi interference and subsequent mRNA degradation of the equivalently delivered *luc* reporter gene; i.e., by direct injection to the muscle, eye, brain, administration to the liver via blood stream injection and administration to the lung by inhalant (see: Examples). However, the specification provides no specific guidance and no examples of methods of treatment, *in vivo*, in a mammal (including humans), comprising reducing the expression or mediating the degradation of mRNA expressed from any target gene, *in vivo*, comprising administration of any rAAV vector of serotypes 1-8 (including homologous serotypes and hybrids thereof) wherein the vector comprises an RNAi expression cassette that expresses an RNA molecule that mediates RNAi interference and subsequent mRNA degradation of essentially any target gene, thereby providing a treatment effect. In particular, Applicant provides no indication of how the claimed method would allow specific targeting of any target gene to provide a treatment effect, *in vivo*, for essentially any disease, commensurate in scope with what is now claimed. Applicant has disclosed the inhibition of expression, *in vivo*, of a transgene that was delivered to a mouse via the same vector and same route of administration as the subsequently administered rAAV vector expressing an RNAi molecule. However, the rAAV vector which delivered the transgene and the RNAi expression cassette would

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be expected to move systemically within the animal (the mouse) in the same manner; i.e., in mammalian cells or in the cells, tissues or organs of a mammal *in vivo*. There is no indication, from the specification as filed, that the method as claimed could employ an rAAV vector, as claimed, to provide a treatment effect, *in vivo*, via the expression of an RNAi molecule, to essentially any cell, thereby providing a treatment effect for essentially any disease by targeting essentially any gene, commensurate with the full scope of the instant claims.

The unpredictability of inhibiting expression of a target gene by RNA interference (RNAi), particularly in regards to the amount of experimentation that would be required to practice the instantly claimed methods in their full scope, is evident from literature that reflects the state of the art at the time of filing. While it is recognized that introduction of dsRNA that is targeted to a specific gene may result in attenuation of expression of the targeted gene, at the time the instant invention was made, the use of a nucleic acid based therapy to provide a specific treatment effect, *in vivo*, via the degradation of a particular mRNA targeted by a particular RNAi molecule was highly unpredictable. Even to date, RNA interference is still recognized in the art as not fully enabled for the broad scope of therapeutic purposes that are instantly claimed.

See for example, the post filing art of Caplen (RNAi as a gene therapy approach. Expert Opin. Biol. Ther. 2003, Vol. 3, pgs. 575-586) which details the unpredictability of any given siRNA to mediate RNA interference of any given gene in mammalian cells and the state of the art of RNA interference for therapeutic purposes. Caplen points out that, "Many of the problems associated with developing RNAi as an effective

therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (pg. 581). Caplen also states that, "While most siRNAs are effective in inducing some degree of gene silencing, there are wide ranges in efficacy of individual siRNAs against sequences within the same gene and some siRNAs show limited or no ability to mediate RNAi. It is currently unclear what specific parameters determine the effectiveness of a given siRNA and thus, why some sequences may be better targets than others" (pg. 577, col. 2, 2nd full paragraph Coburn et al. also points out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph). Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes that therapeutic methods are not yet effective.

The post-filing art also describes the ongoing difficulties in using RNAi to treat disease and the unpredictability involved in specific targeting of any particular mRNA for degradation wherein it describes the results from several laboratories which point to off target effects of any given siRNA and the inefficacy of particular siRNAs, the reasons for which remaining poorly understood (Check, E. Nature, 2003, vol. 425, p. 10-12). Check discloses how in one study by the Rosetta team, a range of different siRNAs targeted to two genes in mammalian cells caused changes in the expression of dozens of other

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genes, these off target effects being seen in a different range of off target genes depending on the precise sequence of the siRNA concerned (pg. 12, col. 1, last paragraph). Check also discloses that in another study, from a group at Case Western University, siRNAs introduced into mammalian cells activated certain genes in the interferon system, a mechanism by which cells shut themselves down in response to invading germs and that the research team involved considers that its findings provide a warning that off target effects are perhaps more common than scientists have realized (pg. 12, col. 2 , bridge to col. 3). In conclusion, Check states that, "Its unclear why some siRNAs are incredibly effective whereas others, targeted at a different region of the same gene, don't work at all (pg. 12, col. 3, 1st full paragraph).

Furthermore, Opalinska et al. (Nature Review, 2002, Vol. 1, p. 503-514) state, "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA" (pg. 511, col. 1). Opalinska et al further state, in regards to that targeting of particular mRNAs, that "In mRNA, sequence accessibility is dictated by internal base pairing and the proteins that associate with the RNA in a living cell. Attempts to accurately predict the *in vivo* structure of RNA have been fraught with difficulty. Accordingly, mRNA targeting is largely a random process, which accounts for the many experiments in which the

addition of an antisense nucleic acid yields no effect on expression" (pg. 511, col. 1 bridge to col. 2).

Given this unpredictability, one of skill in the art would require specific guidance to practice the claimed methods *in vivo* in any mammal, with a resultant therapeutic outcome, as claimed. With regard to the instant application, although delivery of rAAV vectors that mediate the RNA interference of mRNA expressed from an equivalently delivered reporter transgene, in cells that can be targeted by the same mode of administration has been shown, the instant methods as claimed, require delivery to essentially any cell to mediate RNAi of essentially any gene to provide a treatment effect for essentially any disease. The state of the art, however, as evidenced by the references above, is not enabling for the broad scope of method as claimed. Applicant has provided no guidance as to how the claimed methods can be used to target any essentially any cells, organs or tissues, *in vivo*, in a mammal, such that the desired therapeutic effect, of treating essentially any disease, is enabled.

Given the above, one of skill in the art would not know *a priori* whether practicing the instantly claimed methods comprising introduction of an RNAi molecule via an rAAV vector into any mammal *in vivo*, by the disclosed methodologies of the instant invention, would result in the successful decrease in expression of any gene/mRNA in any tissue or organ in said mammal so as to provide a treatment of essentially any disease. In particular, one of skill in the art would not know what particular RNAi molecules, expressed from the claimed RNAi expression cassettes that are delivered by rAAV vectors, to make, that would mediate RNAi of that particular target gene, in any cell,

tissue or organ of any mammal, so as to provide a treatment commensurate with the extremely broad scope of treatments as claimed.

The specification does not provide the guidance required to overcome the art-recognized unpredictability in providing a specific therapeutic effect via the specific delivery of a therapeutic RNAi molecule, *in vivo*, to any mammal, including humans. The field of RNA interference does not provide that guidance, such that any person skilled in the art would be able to practice the claimed therapeutic methods without performing undue trial and error experimentation to characterize and optimize a large number of variable parameters involved in the *in vivo* practice of nucleic acid therapeutics (as outlined above) including, at least, a) the determination of what sequences would constitute efficacious RNAi molecules within the scope of what is claimed.

Thus, while the specification is enabling for methods of inhibiting the expression, *in vivo*, in a mouse, of a rAAV 2/5 delivered *luc* reporter transgene via administration of an rAAV 2/5 vector comprising an RNAi expression cassette that expresses an RNA molecule that mediates RNAi interference and subsequent mRNA degradation of the equivalently delivered *luc* reporter gene; i.e., by direct injection to the muscle, eye, brain, administration to the liver via blood stream injection and administration to the lung by inhalant, does not reasonably provide enablement for the full scope of what is now claimed, which are methods of inhibiting the expression, *in vivo*, of any gene in any mammal, including humans, via administration of any rAAV vector of serotype 1-8 or any homologous serotype or hybrid thereof comprising an RNAi expression cassette

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that expresses an RNA molecule that mediates RNAi interference and subsequent mRNA degradation of any endogenous mRNA because the art of inhibiting gene expression *in vivo*, in mammals, via administration of an RNAi molecule of the invention into a cell or organism is neither routine nor predictable. Therefore, one of skill in the art could not practice the invention commensurate in scope with what is now claimed, without undue, *de novo* trial and error experimentation. Additionally, the type of experimentation required to practice the invention more broadly that is exemplified is a factor in the enablement analysis, but is not dispositive. In this case, even if the nature of each experiment required to expand the scope of the enabled invention was considered standard (which it is not), it would be out weighted by the sheer quantity of experimentation required to practice the full scope of the claimed invention.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

19. Claims 1-6, 12, 14-15, 19-22, 24-32, 35-36, 38-39 and 49-50 are rejected under 35 U.S.C. 102(e) as being anticipated by Tolentino et al. (US Patent Application

Publication 2004/0018176 A1) as supported by US Provisional Application 60/398,417). Instant claims 1 and 2 drawn to methods of decreasing the expression of a target gene *in vivo* in mammals comprising delivery to, cells of a subject, an rAAV vector which allows expression of an RNA molecule that mediates RNA interference. Subsequent dependent claims require further limitations in regards to the structure of and type of the RNAi molecule that is expressed, that the molecule be a short hairpin RNA of a comprising a loop and duplex of specified lengths, hybridization specificities and orientations within a single molecule, target a disease gene wherein that disease gene is subsequently limited to the VEGF gene, employ a pol III promoter in the rAAV vectors used for *in vivo* delivery and require that particular cells that are transduced, *in vivo* (dependent claims 4-6, 12-15, 19-22, 24-32, 35-36, 38-39). Claims 49 and 50 are specifically drawn to methods of treatment of a disease comprising inhibiting the expression of a target gene *in vivo* in mammals, more specifically in a human (claim 50), comprising delivery to, cells of a subject, an rAAV vector which allows expression of an RNA molecule that mediates RNA interference.

Tolentino et al. disclose a method of inhibiting the expression of VEGF in mammals, including humans, comprising administering a recombinant AAV vector that expresses a short hairpin RNA (shRNA) intracellularly wherein the expressed shRNA comprises 2 self complementary 19-25 bp regions joined by a loop wherein one of the regions is antisense and fully complementary to a target gene wherein the target gene is VEGF, the other region is fully complementary to the first region and the cells of the subject that are transduced are cells of the eye. The disclosure of Tolentino et al. is

considered an inherent disclosure of a loop that is about 2 to about 10 nucleotides because a reasonable interpretation of the disclosure, which does not explicitly set forth the size of the loop in the viral expression construct, considers that it reads on all loop sizes, including a minimal loop of about 2 nucleotides. Tolentino et al. disclose a table of target sequences that are targeted by the RNAi molecules of their invention and that these sequences are common to all alternative human VEGF splice variants. The rAAV vectors disclosed by Tolentino et al. comprise pol III promoters (*please see the following sections of Tolentino et al.*: pg. 2; [0015], [0025-0026]; pg. 3-4, [0042]; pg. 6, [0059-0069]; pg. 7, [0080],[0082]; pg. 8, [0093-0095] and pgs 10-11, Examples 4-7). Therefore, Tolentino et al. anticipate the instant invention as set forth in the above claims.

Conclusion

20. No claims are allowed.

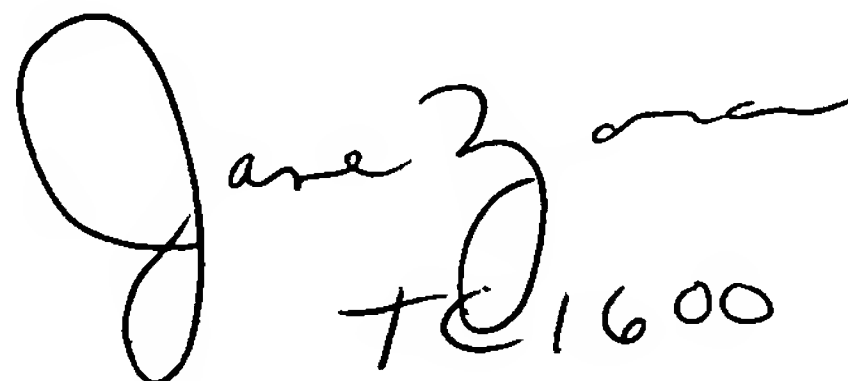
21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon B. Ashen whose telephone number is 571-272-2913. The examiner can normally be reached on 7:30 am - 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Jba



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